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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/218,660 12/22/98 UNGER

UNGR-1520

EXAMINER

HM22/0718

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ART UNIT

PAPER NUMBER

1619

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/218,660

Applicant(s)

Unger et al

Examiner
Shahnam Sharareh

Group Art Unit
1616



☒ Responsive to communication(s) filed on Jun 5, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 100-103, 113-115, 122-124, 127, and 194-356 is/are pending in the application.

Of the above, claim(s) 204-209, 239-244, 271-276, 304-309, and 341-346 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 100-103, 113-115, 122-124, 127, 194-203, 210-238, 245-270, 277-303, and 310-340, 342-356 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4-6, 10

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Art Unit: 1616

DETAILED ACTION

Amendment filed on November 15, 1999 has been entered. Accordingly, claims 1-99, 104-112, 116-121, 125-126, 128-193 have been canceled, and claims 194-356 have been added. Claims 100-103, 113-115, 122-124, 127, 194-356 are now pending.

Applicant's election of Group II, and the species of (a) lipid vesicles formulated from one or more phospholipids, (b) perfluorobutane gas, (c) a targeting ligand which comprise a peptide including the amino acid sequence arginine-glycine-aspartic acid (d) and the Glycoprotein GPIIb/IIIa receptor is acknowledged. Since Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)), and is made **Final**.

Claims 204-209, 239-244, 271-276, 304-309, 341-346 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Applicant is noted that claims 100-103, 113-115, 122-124, 127, 194-203, 210-238, 245-270, 277-303, 310-340, 347-356 are directed to the elected invention.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Amendment filed on May 5, 2000 has been entered. The submitted CRF is in good order and complies with the sequence listing requirement.

Art Unit: 1616

Priority

1. The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

In the instant case, the U.S. application Serial No.08/660,032, filed June 6, 1996, now abandoned, the U.S. application Serial No. 08/640,464, filed May 1, 1996, now abandoned, the U.S. application Serial No. 08/497,684, now abandoned, fail to teach compositions comprising gaseous lipid vessels in combination with a targeting moiety such as an Arginine-Glycine-Aspartic acid directed to a glycoprotein receptor such as GPIIbIII; or methods of lysing a thrombus utilizing an ultrasonic method of drug delivery comprising administering to a patient targeted vesicle compositions encapsulating a gas, and scanning the patient with a ultrasonic source. Thus, the effective priority date used for the examination of the instant application is December 22, 1998.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

Art Unit: 1616

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 100-103, 113-115, 122-124, 194-201, 210, 214-215, 217-220, 223-233, 236, 245, 249-252, 255-268, 277, 281-284, 287-301, 310, 314-317, 320-338 are rejected under 35

U.S.C. 102(e) as being anticipated by Lanza et al US Patent 5,989,520.

The instant claims are drawn to targeted compositions and formulations comprising a bioactive agent, a perfluorocarbon gas, a lipid wall, and a targeting moiety. The instant claims are also directed to methods of drug delivery comprising (I) administering to a patient a composition comprising said compositions; and (II) scanning the patient using ultrasound waves, wherein the vesicle comprising targeting agents to a specific cell surface receptor. The claims are also directed to methods of preparing said compositions.

Lanza et al disclose liposomal compositions comprising a perfluorocarbon gas, a bioactive agent, a phospholipid wall, and a targeting moiety (see col 5-7, specifically col 7 lines 41-52, examples 1-4.) Lanza also disclose the use of various suitable therapeutic agents, such as streptokinase, or gene therapy delivery system combined with ultrasonic imaging, as well as the methods of preparing and using thereof (see col 7 lines 19-41, and lines 60-68, example 18.) The instant open-ended claims comprise and do not exclude any components essential to the operability of the cited prior art patents. Applicant is informed that the compositions of Lanza meet the structural limitations of the instant formulations and target delivery systems, therefore, they also inherently possess the functional characteristics of the instant invention. In addition, a

Art Unit: 1616

recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making or using, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Accordingly, Lanza et al meets the limitations set forth in the instant claims.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1616

Claim 100-103, 113-115, 122-124, 127, 194-203, 210-238, 245-270, 277-303, 310-340, 347-356 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishioka et al (J AM Cardiol 1997; 30:561-8) in view of Lanza et al 5,989,520, Schutt et al US Patent 5,626,833, Konigsberg et al US Patent 5,284,499, EP 0 422 938 and Ishihara US Patent 5,190,766.

The instant claims are drawn to targeted compositions and formulations comprising a bioactive agent, a perfluorocarbon gas, a lipid wall, and a targeting moiety. The instant claims are also directed to methods of drug delivery comprising (I) administering to a patient a composition comprising said compositions; and (II) scanning the patient using ultrasound waves, wherein the vesicle comprising targeting agents to a specific cell surface receptor. The claims are also directed to methods of preparing said compositions.

Nishioka et al disclose the use of microbubbles contrast agents, dodecafluoropentane (DDFP) emulsion, to enhance low frequency ultrasound clot disruption in vivo (see abstract.) Nishioka et al teach that the direct thrombolytic and combined effect of DDFP with transcutaneous ultrasound significantly enhance the clot dissolution when compared to placebo or saline alone; and further that said combination would improve clinical management of patients suffering from thrombotic arterial occlusions (see Fig 1, discussion.) Finally, Nishioka distinctively suggests that the use of a tissue (thrombus)-targeted contrast agent, as reported by Lanza et al, might be worth utilizing to enhance specific targeting of the area of interest (see page 567 paragraph 3 line 9-14.) Nishioka et al fail to specifically use a liposomal contrast agent.

Art Unit: 1616

The concept of enhancing liposomal specificity by conjugating liposomes to a ligand such as a peptide, a lipid, or a nucleic acid is well known in the art and has also been described by Lanza et al US Patent 5,989,520, the teaching of which is discussed above. Furthermore, it is well known in the art how to modify carriers such that they are bound, ionically or covalently, to a ligand that binds to a cell surface receptor. For example, Konigsberg et al in US 5,284,499 describes the incorporation of receptor specific ligands into Liposomes, which are then used to target receptors on the cell surface. Therefore, it is well settled in the art that preparing targeting Liposomes to create more specific delivery systems is conventional.

EP 0 422 938 disclose the synthetic alpha-amino acid containing chains of RGD that are specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor the utility of which as a targeting ligand has been well established in the art.

Ishihara et al disclose a method of drug delivery comprising administering an encapsulated gas microcapsule (such as a liposome or albumin), and irradiating the patient with ultrasonic waves. Ishihara further disclose measuring the acoustic characteristics of the microcapsule as well as the preferred resonant frequency (1.5-2.0 MHZ) that can be used to release the drug from the microcapsules (see col 1 lines 19-49, col 4 lines 13-68, col 5 1-50, col 6 lines 37-68, col 7 lines 33-68, col 10 lines 3-47, claims 1-6.) Ishihara does not fully disclose a targeted vessel.

Schutt et al disclose various types of perfluorinated microbubbles for use as ultrasound contrast agent comprising phospholipid containing walls (see claims 1-10.) Schutt et al further

Art Unit: 1616

indicate that the use of their perfluorocarbon containing compositions can enhance the thrombolytic activity of agent such as TPA or Streptokinase (see col 11, lines 18-30.)

Nishioka, Lanza, Schutt, and Ishihara teach the utilization of ultrasonic waves and gas vesicles in the field of sonodynamic therapy. Thus, the teachings of all are viewed as being in the same field of endeavor. Further, EP patent show the general knowledge in the art about the utility of RGD aminoacid chain which is recognized in the art as a targeting agent.

Nishioka et al do not specifically disclose methods of drug delivery or therapy utilizing glycoprotein targeted vessel comprising a liposome; however, to minimize the systemic adverse affects, as suggested by Nishioka, one skilled in the art would have been motivated to utilize the teachings of Lanza, Schutt and the EP Patent to make targeted perfluorinated gaseous liposomes, as disclosed by Lanza, and further apply the ultrasonic sonotherapy of Ishihara to maximize the local drug delivery, while minimizing the systemic adverse effects. Accordingly, methods of making and using such drug delivery systems would have also been obvious.

The policy of the US PTO is to give pending claims their broadest reasonable interpretation. The instant open-ended claims comprise and do not exclude any components or method steps essential to the operability of the cited prior arts. Furthermore, differences in ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such ranges (such as the instant rate of administration) is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Art Unit: 1616

Finally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose the idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven , 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) Therefore, one ordinary skilled in the art would have been motivated at the time of invention to combine the teachings of Nishioko, Lanza, Schutt and the EP Patent, because he would have had a reasonable expectation of success, as suggested by Nishioko, to improve the clinical management of patients with thrombotic arterial occlusion when combining transcutaneous ultrasound and a targeted delivery system comprising a perfluorocarbon gas. Finally, it is well within purview of an ordinary skilled artisan to optimize the binding affinity of the targeted delivery system to establish the optimal method of treatment.

Information Disclosure Statement

4. The information disclosure statement filed March 18, 1999 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. In this case, the references AC, AD, AE are not considered.

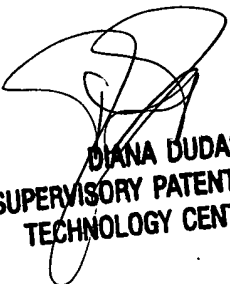
In addition, it is noted that Applicant is merely citing various handbooks of which no concise explanation of relevance is provided. Accordingly, said citations do not comply with with 37 CFR 1.98(a)(3). Applicant is encouraged to provide copies of relevant information pertaining to the instant invention.

Art Unit: 1616

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

sjs 7/14/00


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